

# Methods for a Public Health Response to Birth Defects Clusters

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**ABSTRACT** Few resources are available to guide public health officials in investigations of reported birth defects clusters. The majority of published resources focus on the investigation of cancer and infectious disease clusters and do not address clinical and epidemiologic concerns specific to birth defects research. This document aims to address these concerns, discuss the needs of the affected community, and provide suggestions for the development of a standardized protocol to be used as a guide in the investigation of birth defects clusters. We suggest that health departments and birth defects registries that may receive reports of birth defects clusters establish a protocol for responding that includes the following steps: develop a proactive plan for future birth defects cluster reports (step I), receive report of a birth defects cluster (step II), verify diagnoses and complete case ascertainment (step III), compare the observed rate to a reference rate (step IV), ascertain exposures among cases from available records (step V), interview case mothers (step VI), initiate further epidemiologic study—selection of controls (step VII), and communicate results to the community (step VIII). Specific criteria for continuing or terminating an investigation should be established before receiving cluster reports. The recommendations in this report should be carefully considered to ensure that the specific needs of the region, agency and affected community are met. *Teratology* 66:S50–S58, 2002. Published 2002 Wiley-Liss, Inc.<sup>†</sup>

## INTRODUCTION

Clusters of birth defects are reported frequently in the United States. However, limited resources are available that describe a standard protocol for these investigations. In 1990, the American Journal of Epidemiology published a supplement that included methodologic examinations and examples of cluster investigations, most of which were derived from cancer cluster research (Fiore et al., '90; Beral, '90; Osborne III et al., '90; Turnbull et al., '90; Williams et al., '90). Also in 1990, the Centers for Disease Control and Prevention (CDC) proposed guidelines for non-infectious disease cluster investigations (CDC, '90). However, these reports do not address the clinical and epidemiologic considerations specific to birth defects research. Several papers were published in a 1999 issue of the Eu-

ropean Journal of Epidemiology that discussed the history of birth defects cluster investigations, spatial variation analyses, and methods for investigation (Goujard, '99; De Wals, '99; Dolk, '99). These papers provide useful information and examples of birth defects cluster investigations but again, do not discuss the unique characteristics of birth defects research. Some birth defects surveillance systems have internal protocols that address the needs and resources available in their own region, but these have not been published in the scientific literature (Wynne et al., '99; TBDMD, '99).

This report can assist state and local health departments or birth defects surveillance systems in the investigation of birth defects clusters by providing definitions and recommendations to aid in the development of a standardized protocol (Fig. 1); considerations specific to the needs of the affected community are also discussed. This report does not make recommendations about the specific criteria for continuing or terminating an investigation but does recommend that these criteria be established by the investigating agency prior to receiving cluster reports.

## BACKGROUND

A birth defects cluster is a real or perceived aggregation of more than the expected number of birth defects cases in a population over a specified time period (Wynne et al., '99). Birth defects rates fluctuate in populations over time, which can create the appearance of clusters. For example, cleft lip with or without cleft palate occurs in approximately one in 1000 births (NBDPN, 2001). If a population has 30,000 births per year, 30 cases would be expected annually. However, because of normal fluctuations, 33, 25, or even 40 cases may occur. Increases in the rates of birth defects should occur as frequently as decreases within a population. Birth defects surveillance systems can serve as important resources when investigating these occurrences because they monitor birth defects rates in a defined population over time.

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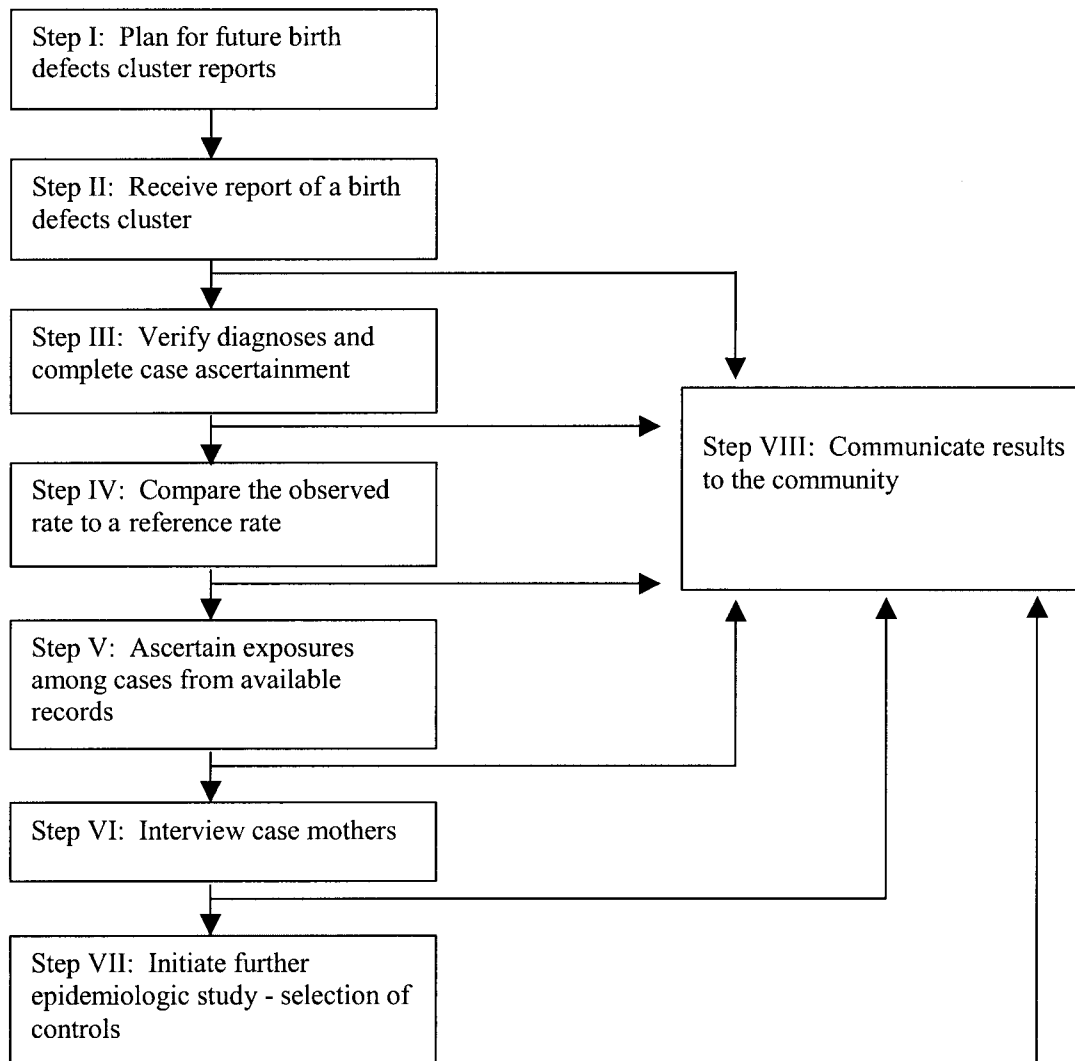


Fig. 1. Sample protocol for investigating birth defects clusters

Changes in diagnostic practices or hospital referral patterns can also create the appearance of birth defects clusters. In the late 1970s and early 1980s several clusters of craniosynostosis were reported to the Colorado Department of Health (CDH). An investigation determined that the reported clusters were indicative of an increased prevalence of craniosynostosis in Colorado; however, no environmental cause for these clusters was apparent (CDC, '87). A surveillance system for craniosynostosis cases was established and available case-patient radiographs were reviewed to confirm the diagnosis. This review suggested that 49 percent of the cases did not meet the case definition for craniosynostosis; investigators concluded that the increase in the prevalence of craniosynostosis was due to differences in diagnostic criteria (Alderman et al., '97).

Local and state health departments and other agencies have routinely investigated cluster reports; however, the majority of these efforts have not revealed any conclusive findings (Fiore et al., '90; Bender et al., '90;

Caldwell, '90). The lack of conclusive findings and mounting resources required for investigations prompted the CDC in the mid-1980s to discontinue devoting full-time staff to researching cancer cluster investigations (CDC, 2001). These experiences have extended to birth defects clusters as well. The California Birth Defects Monitoring Program has investigated over 140 reports of birth defects clusters since 1983; 95% of those investigations determined that no excess of cases occurred (Wynne et al., '99).

Despite the many inconclusive findings, clusters can occur because of a shared exposure, and some investigations have made substantial contributions to public health. For example, a cluster of pneumonia at an American Legion convention in Philadelphia identified a new disease-causing bacterium *Legionellae* (Fraser et al., '77), a cluster of *Pneumocystis carinii* pneumonia among five homosexual men living in Los Angeles led to the identification of acquired immunodeficiency syndrome (AIDS) and the human immunodeficiency virus

(HIV) (CDC, '81), and a cluster of vaginal clear cell adenocarcinoma identified a causal relationship between diethylstilbestrol (DES) exposure during pregnancy and this outcome among female offspring (Herbst et al., '71).

Additionally, pediatric and perinatal cluster investigations have led to the discovery of important etiologic associations including the association between thalidomide ingestion during pregnancy and phocomelia (McBride, '63). A more recent example occurred in March 1999 when pediatric surgeons in Knoxville, Tennessee noted an increase in cases of infantile hypertrophic pyloric stenosis (IHPS) with seven cases occurring in a two-week period. They also noted that all seven cases had been born in the same birth hospital and had taken oral erythromycin for pertussis prophylaxis. This cluster created a high index of suspicion because all cases shared an exposure (oral erythromycin) that is relatively rare among the general population of neonates. The initial investigation confirmed a nearly seven-fold increase in the occurrence of IHPS compared to the previous two years. A retrospective cohort study of infants born at the same birth hospital during January and February 1999 confirmed an association between oral erythromycin and IHPS (Honein et al., '99). Following publication of these findings, the American Academy of Pediatrics (AAP) changed their recommendations and no longer recommend that erythromycin be given to asymptomatic infants born to women with untreated chlamydial infections. The AAP still recommends oral erythromycin for the treatment of chlamydial conjunctivitis and pneumonia in young infants and to prevent pertussis in young infants who have been exposed, but advises informing parents about the potential risk of developing pyloric stenosis (AAP, 2000).

### Methods for investigating birth defects clusters

Birth defects surveillance systems are limited in their ability to detect teratogens (Khoury and Holtzman, '87). Cluster investigations may be an alternative resource in determining disease etiology and also have an important role in addressing community concerns. Errors in defining the defect(s), population, time frame, or exposure in a cluster investigation can lead to a spuriously defined cluster or a true cluster not being identified. Birth defects clusters present unique challenges, including difficulties in case classification, problems in case ascertainment, particularly for stillbirths and pregnancy terminations, and limited current information on the etiology of most defects. The following steps address these and other concerns and can be used as a guide when developing a protocol for investigating clusters of birth defects.

#### Step I: Plan for future birth defects cluster reports

Resource allocation within a region may determine who should lead cluster investigations. We recommend that one agency, such as a state health department or birth defects registry, be selected to investigate birth

defects cluster reports. Identifying a central investigating agency and developing a standardized protocol can save time and resources and can avoid confusion. This decision should be communicated to all other related agencies so that appropriate referrals can be made.

The designated agency should organize needed resources prior to receiving cluster reports. A data-abstraction form should be developed to aid with case and exposure ascertainment; example forms can be obtained from birth defects registries or the CDC. Establishing a system or database to store abstracted information is also useful as it can be used to monitor the progress of investigations and can act as a reference if requests are made by individuals, media, or other groups.

The investigating agency should respond each time a cluster report is made. The level of this response will be determined by the information available about the suspected cluster and the predetermined criteria established within the agency. A consistent approach can help ensure that the decisions are made scientifically to the extent possible. This could be specified as an absolute number of cases with the same defect(s) and exposure or could be based on a combination of factors, including the elevation of the prevalence over background levels, plausibility of the exposure, and the differential in exposure prevalence between the cases in the cluster and the general population. Each step in a protocol should provide an opportunity to reevaluate the information available and determine if the investigation should continue or be terminated. These decisions should be communicated to the reporting individual or agency; the protocol can be referenced during this exchange to provide justification for a decision (See Step VIII: Communicate results to the community). It is important to remember that internal criteria should remain flexible. There may be extenuating circumstances, such as political or social concerns, surrounding a suspected cluster that suggest an investigation may be appropriate even if the data do not meet the predetermined criteria.

#### Step II: Receive report of a birth defects cluster

Reports of clusters may come from an affected community, health-care provider, or from another agency. When a report is made, the information should be transferred onto a standard reporting form. This form should ascertain as much information as possible about each case including the diagnoses, contact information for each case-patient (e.g., name, address, telephone number, hospital of delivery, or local physician), and any exposures of concern. The person or agency reporting the cluster should be asked to provide sufficient information about the suspected cluster to determine if continued investigation is warranted. If informants cannot provide sufficient information, they should be encouraged to ascertain more information or to have a more knowledgeable person contact the investigating agency.

As described in Step I, the criteria used to continue or terminate an investigation should reflect the available data and resources within the agency. For example, the California Birth Defects Monitoring Program criteria dictate that a cluster investigation should continue after the initial report if there are at least three cases with the same defect or developmentally related defects, if adequate information has been provided in the initial report to verify the cases, time period, and population, and if there is not another apparent explanation (Wynne et al., '99). Programs with limited resources may consider comparing the observed rate to an expected rate at this point in the investigation (see Step IV: Compare the observed rate to reference rate). We recognize that each agency has different available resources; it is important that agencies determine the appropriate criteria for their own setting.

If the information provided from the initial report does not meet the established criteria to continue with an investigation, results should be appropriately communicated to the community (see Step VIII: Communicate results to the community).

### **Step III: Verify diagnoses and complete case ascertainment**

A case definition that includes type of defect(s), population or geographic area, and time period should be established. With regard to the type of defect(s), in most cases, defects should either be the same or pathogenetically similar. In some situations, the delineation of pathogenetically similar defects is clear (e.g., neural tube defects), but sometimes this may be less evident. For example, gastroschisis, porencephaly, and hydranencephaly all are postulated to have a similar pathogenesis related to prenatal vascular disruption (Lubinsky, '97). Case-patients with multiple birth defects deserve additional consideration. Because teratogens often cause certain patterns of defects (Polifka and Friedman, '99), cases of multiple birth defects should be explored further to determine if a pattern exists. Therefore, review of cases by a clinical geneticist with expertise in birth defects may be advantageous. When available, birth defects surveillance system, health department agency, and vital statistics records can be used to confirm diagnoses and ascertain other pertinent information. When no surveillance system is available, medical records for all case-patients should be reviewed, including hospital records, cytogenetic analyses, outpatient clinic records, and other relevant records. Information about associated syndromes should be collected because an isolated birth defect (e.g., cleft lip) and a birth defect associated with a recognized syndrome (e.g., Trisomy 13 with a cleft lip) have different etiologies and therefore are unlikely to have a unifying cause in a cluster. If medical record review is performed, exposure information available in the medical record can be ascertained simultaneously (see Step V: Ascertain exposures among cases from available records).

Depending on the type of diagnosis, new referral patterns or changes in diagnostic practice may result in an apparent cluster. Therefore, independent verification of the diagnosis may be necessary. The importance of this verification is illustrated by the previously mentioned investigations of apparent clusters of craniosynostosis observed in Colorado (Alderman et al., '97). In this study, only 51% of the cases were found to have radiographically verified craniosynostosis. In contrast, in the investigation of pyloric stenosis and erythromycin exposure, the ultrasonographic diagnoses were validated by an independent pediatric radiologist who reviewed both positive and negative ultrasonographic scans for pyloric stenosis from the same hospital as the original cases (Honein et al., '99). One hundred percent agreement was observed between the diagnoses by the hospital radiologist and the independent radiologist.

For some defects, methods of diagnosis may be included in the case definition. For example, a ventricular septal defect diagnosed only by auscultation may not be included; diagnosis by a more definitive method (e.g., echocardiography, cardiac catheterization, surgery, or pathology) may be required. Case definitions should also include age at which the defect is diagnosed (e.g., before one year) and whether prenatally diagnosed cases will be included. In deciding whether to include prenatally diagnosed cases, several issues must be considered. First, one must consider how frequently the defect is expected to be diagnosed prenatally. Excluding prenatally diagnosed cases for some defects will substantially lower the number of cases observed (Roberts et al., '95). Other issues include whether the defect can be diagnosed prenatally with a degree of certainty and whether prenatally diagnosed cases are included in the case-population (such as the region's birth defects surveillance system) to be used for comparison.

Once the index cases have been verified using the case definition, identification of additional cases that meet the case definition that were not included in the initial report is needed. Cases can be ascertained through birth defects surveillance systems, if available, or through a review of hospital discharge records, patients seen in specialty clinics (e.g., obstetrics, genetics, pregnancy termination, and cardiology), and laboratory results.

**Population and time frame:** The two remaining aspects of a case definition include the determination of the population from which cases arose and the time frame during which they occurred. Typically the population chosen is the smallest population that includes the cases involved in the cluster for which adequate denominator data are available. The mother's address at the time of birth or time of conception may be used to define the population. Olsen et al. ('96) have discussed a problem with the definition of population and time period in cluster investigations called "boundary tightening". The more narrowly a population is defined (geographically and by time period), the smaller the



number of expected cases, which increases the likelihood that an excess number of cases will be observed in the area. When developing a case definition, the population and time frame chosen must be adequate to provide statistically reliable rates. For example, the investigation could be limited to infants born to mothers who were residents of a particular county at the time of delivery over a period of several months or years. Power calculations can be done using the Statistical Analysis Battery for Epidemiological Research (SABER), which is available on CDC's website (<http://www.cdc.gov/ncbddd/bd/saber.htm>), to determine the precision of estimates that will result from using a given population size. This can guide decisions on the population inclusion criteria to be used for a particular investigation.

If the information provided does not meet the established criteria to continue with an investigation, results should be appropriately communicated to the community (see Step VIII: Communicate results to the community).

#### **Step IV: Compare the observed rate to a reference rate**

*Calculating an observed rate:* Typically the denominator used in birth defects studies includes live births but excludes stillbirths and pregnancy terminations, even when these subgroups are included in the numerator. This is partially because in most areas data on stillbirths and pregnancy terminations are not reliably ascertained. In addition, among all births, stillbirths and pregnancy terminations constitute a small proportion; therefore, the impact of using only live births in the denominator on birth defects rates is minimal.

If possible, a reference rate from the birth defects surveillance system should be identified. This helps to ensure that the reference population is similar to the observed population. The prevalence of some birth defects varies by race, socioeconomic status, maternal age, and other demographic factors. Choosing an inappropriate comparison group may impair the ability to determine whether an excess of cases has occurred. If a surveillance system is not available in the region, reference rates can be obtained from other population-based surveillance systems that are determined to have a similar population to the one of interest and are considered reliable. Data from the National Birth Defects Prevention Network (NBDPN, 2001) can be used to identify reference rates.

The SABER program can be used to calculate an observed to expected ratio and confidence intervals. An example of this type of calculation comes from a suspected cluster of gastroschisis in metropolitan Atlanta. In 1988, 17 cases of gastroschisis were observed by the Metropolitan Atlanta Congenital Defects Program in a population of 36,648 annual births resulting in a prevalence of 4.6 per 10,000 births. The prevalence of gastroschisis from the previous five years was 1.95 per 10,000 births. When the baseline prevalence was multiplied by the birth population during 1988, the ex-

pected number of cases for 1988 was found to be seven. Inputting 17 observed and seven expected cases results in an O/E ratio of 2.4 with 95% confidence limits of 1.4 to 3.9. This interval excludes one, thus the observed number of cases is statistically higher than expected (MACDP data, unpublished).

If the information provided does not meet the established criteria to continue with an investigation, results should be appropriately communicated to the community (see Step VIII: Communicate results to the community).

#### **Step V: Ascertain exposures among cases from available records**

Once cases have been reviewed to ensure that they meet the case definition for the investigation, investigators should ascertain any relevant exposures that the case-patients may have in common. This process begins with a complete review of the case-patients' medical records for indication of biologically plausible exposures. This may have been done earlier in the investigation if medical records were reviewed, but if not, should be completed at this step. Based on the type of birth defect(s) observed in the cluster, the data collected may vary. Known risk factors for the defect(s) in question should be identified from the literature and data on these factors should be collected.

Beginning exposure ascertainment with a medical record review can be advantageous. First, the medical records should be readily available because they were used to confirm the case diagnoses. Second, medical records often include valuable information on family history of the condition, prescriptions, and other reported exposures that the clinician or parent thought might be relevant to the diagnosis, pregnancy history (e.g., complications, mother's prior pregnancies, birth weight, and gestational age at delivery), and potentially relevant demographic information (e.g., maternal and paternal age, race, and occupation). Additionally, reviewing medical records avoids burdening case-mothers during the initial assessment phase. A case-abstraction form can be used to detail standard information from each medical record. However, abstractors should be advised to review the medical record carefully and note other unusual factors that are not on the standard abstraction form because many birth defects have few or no known risk factors. Other methods of exposure ascertainment may be required if a specific environmental exposure is a concern in the cluster investigation.

If the information provided does not meet the established criteria to continue with an investigation, results should be appropriately communicated to the community (see Step VIII: Communicate results to the community).

#### **Step VI: Interview case mothers**

If the mothers of the case-patients are available, resources permit, and this phase is warranted by the health department's pre-determined policy, a maternal

interview should be considered. Based on the defects being investigated, investigators should identify the time frame of interest when an exposure could be expected to have a causal role in development of the defects. For some defects with a completely unknown etiology, this may include the period from one month before pregnancy through the entire pregnancy. For other defects, a narrower time frame exists for when an exposure could plausibly cause or contribute to the defects; outside expertise may be needed for this determination. During the interview, mothers should be asked about any exposures they recall in the relevant time period, any exposures that they are particularly concerned about, any family history of this specific birth defect or any other birth defects, and any relationship to the other case-patients either through a shared maternal exposure or a familial relationship. To protect confidentiality, the investigator should not divulge identifying information about other cases during the interview. These data can be collected using either an unstructured or structured maternal interview (e.g., the National Birth Defects Prevention Study (NBDPS)) (Yoon et al., 2001). The NBDPS study conducts this as a computer assisted telephone interview; however, a hard copy version of this instrument can be obtained from CDC's National Center on Birth Defects and Developmental Disabilities.

Once the available exposure information on case-patients has been collected, it should be reviewed to identify exposures occurring in most case-patients. Exposures identified as potential causal agents should be evaluated with respect to biologic plausibility, frequency in the general population, and proportion of cluster cases exposed. Exposures that occur in most case-patients but are very rare in the general population should raise the highest index of suspicion. Identifying cases and examining exposure information without selecting controls from the same population is not generally recommended as populations can differ in exposure frequencies; however, in the case of cluster investigations, this method can promote resource efficiency because rare exposures that are shared by the majority of cases in a cluster are likely to be noticed by investigators even without a direct comparison to controls.

If the information provided does not meet the established criteria to continue with an investigation, results should be appropriately communicated to the community (see Step VIII: Communicate results to the community).

#### **Step VII: Initiate further epidemiologic study—selection of controls**

A table detailing the power for possible case-control studies of clusters has been included to assist health departments in determining the utility of proceeding with an epidemiologic investigation (Table 1). Data are presented for the selection of two, three, and four controls per case-patient; the selection of more than four controls per case does not substantially improve power

(Fig. 2). The alpha-level or type I error is the probability of incorrectly rejecting the null hypothesis of no association or no effect, meaning the probability of stating there is an association when in fact there is no association between the exposure and the outcome. By convention, the alpha-level has been set to 0.05 for all the power calculations included. The beta-level or type II error is the probability of accepting the null hypothesis when it is in fact false, meaning the probability of stating that there is no association between an exposure and outcome when in fact there is a true association. By convention, the beta-level should be no more than 0.2, which is equivalent to 80% "power". Typically, when designing an epidemiologic study, one would set the alpha- and beta-levels, specify the prevalence of exposure in the case and control group, and then determine what sample size is required. However, in the case of cluster investigations, the total number of cases is usually very small, and will be the limiting figure in these power calculations.

Once the cases have been classified and the exposures among cases assessed (Steps III to VI), the public health official responding to the cluster should utilize power calculations (Table 1) as a predictor of whether any further epidemiologic investigation is warranted. If resources are available for further study, public health officials should consider recruiting an appropriate control group when the number of cases, prevalence of an exposure among cases, and prevalence of the exposure among controls indicate at least 80% power for the study. This determination will require some assumptions (e.g., prevalence of exposure among controls) based on available information. Additional power calculations may be done using SABER. However, if a rare exposure is identified among the cases, investigators may want to consider the resources required to recruit a control population in light of the potential benefit gained from a traditional case-control study.

If the decision is made to recruit a control group, an appropriate control group must be selected to obtain unbiased estimates of the association between exposure and outcome. The control subjects should be selected randomly from the same source population as the cases and must be selected independent of their exposure status (Rothman and Greenland, '98). The use of a convenience sample of controls should be avoided when resources permit as these are unlikely to be representative of the source population, and their use could result in biased estimates of effect. Appropriate selection of controls will ensure that the substantial resources expended in recruiting and interviewing control subjects are appropriately allocated.

#### **Step VIII: Communicate results to the community**

This step should be part of every cluster investigation, both during the investigation and at its conclusion. The purpose of cluster investigations is not only to potentially identify new teratogens but also to respond to the needs of the affected community. The identifica-

**TABLE 1. Power for assessing clusters of 3 to 7 cases with varying exposure prevalences among cases and controls, assuming alpha = 0.05\*. All scenarios with adequate power (>80%) to detect an effect, assuming there is a true association, are listed in bold type.**

Prevalence of exposure among cases	Prevalence of exposures among controls	Number of cases	Odds ratio	Power 2 controls per case	Power 3 controls per case	Power 4 controls per case
67% (2/3)	15%	3	11.5	34%	41%	46%
67%	25%	3	6.1	22%	25%	28%
67%	50%	3	2.0	6%	7%	7%
75% (3/4)	15%	4	17.0	54%	63%	69%
75%	25%	4	9.0	37%	42%	46%
75%	50%	4	3.0	11%	12%	12%
50% (2/4)	15%	4	5.7	26%	31%	35%
50%	25%	4	3.0	14%	16%	18%
80% (4/5)	15%	5	22.7	74%	<b>82%</b>	<b>86%</b>
80%	25%	5	12.0	53%	61%	65%
80%	50%	5	4.0	17%	18%	19%
80%	75%	5	1.3	4%	4%	4%
60% (3/5)	15%	5	8.5	43%	51%	55%
60%	25%	5	4.5	26%	30%	33%
60%	50%	5	1.5	5%	6%	6%
83% (5/6)	15%	6	27.7	<b>87%</b>	<b>92%</b>	<b>95%</b>
83%	25%	6	14.6	68%	76%	80%
83%	50%	6	4.9	24%	26%	27%
83%	75%	6	1.6	5%	5%	5%
67% (4/6)	15%	6	11.5	61%	69%	74%
67%	25%	6	6.1	40%	46%	50%
67%	50%	6	2.0	9%	10%	10%
50% (3/6)	15%	6	5.7	36%	42%	46%
50%	25%	6	3.0	19%	22%	24%
86% (6/7)	15%	7	34.8	<b>95%</b>	<b>98%</b>	<b>99%</b>
86%	25%	7	18.4	<b>82%</b>	<b>88%</b>	<b>91%</b>
86%	50%	7	6.1	33%	36%	38%
86%	75%	7	2.0	7%	6%	6%
71% (5/7)	15%	7	13.9	75%	<b>82%</b>	<b>86%</b>
71%	25%	7	7.3	53%	60%	64%
71%	50%	7	2.4	14%	15%	15%
57% (4/7)	15%	7	7.5	52%	59%	64%
57%	25%	7	4.0	30%	35%	38%
57%	50%	7	1.3	5%	5%	5%

\*Statistical Analysis Battery for Epidemiological Research (SABER) was used for all power calculations (<http://www.cdc.gov/ncbddd/bd/saber.htm>).

tion of a cluster, whether real or perceived, can create fear and anxiety. An agency's active response to cluster reports and open communication with the affected community can help establish trust between the community and the investigating agency. The investigating agency needs to understand the community's concerns and respond appropriately to relieve the stress and uncertainty associated with perceived clusters. Several misperceptions about clusters should be addressed sensitively with the community early in the investigation. First, the general public tends to perceive birth defects to be extremely rare, resulting in an expectation that every baby should be healthy. Although birth defects are rare events, some are more common than the general public may perceive (Table 2); one in 33 babies born in the United States will be affected by a major birth defect (Lynberg and Edmonds, '92).

Second, although the community may be concerned about a particular environmental agent, investigators should clarify that many environmental exposures are difficult or impossible to measure given current knowledge and available technology. Even if an excess of cases were identified, it may not be possible to identify the etiologic link between the cases. However, investigators should actively listen to, and take seriously, the community's concerns about potential exposures. This can help to build a rapport between the community and investigator, which is essential to conducting an effective investigation. The association between DES exposure and vaginal clear cell adenocarcinoma was sparked by voluntary maternal reports of exposure during interviews (Herbst et al., '71).

Third, the public often perceives that cluster investigations should be able to be conducted quickly

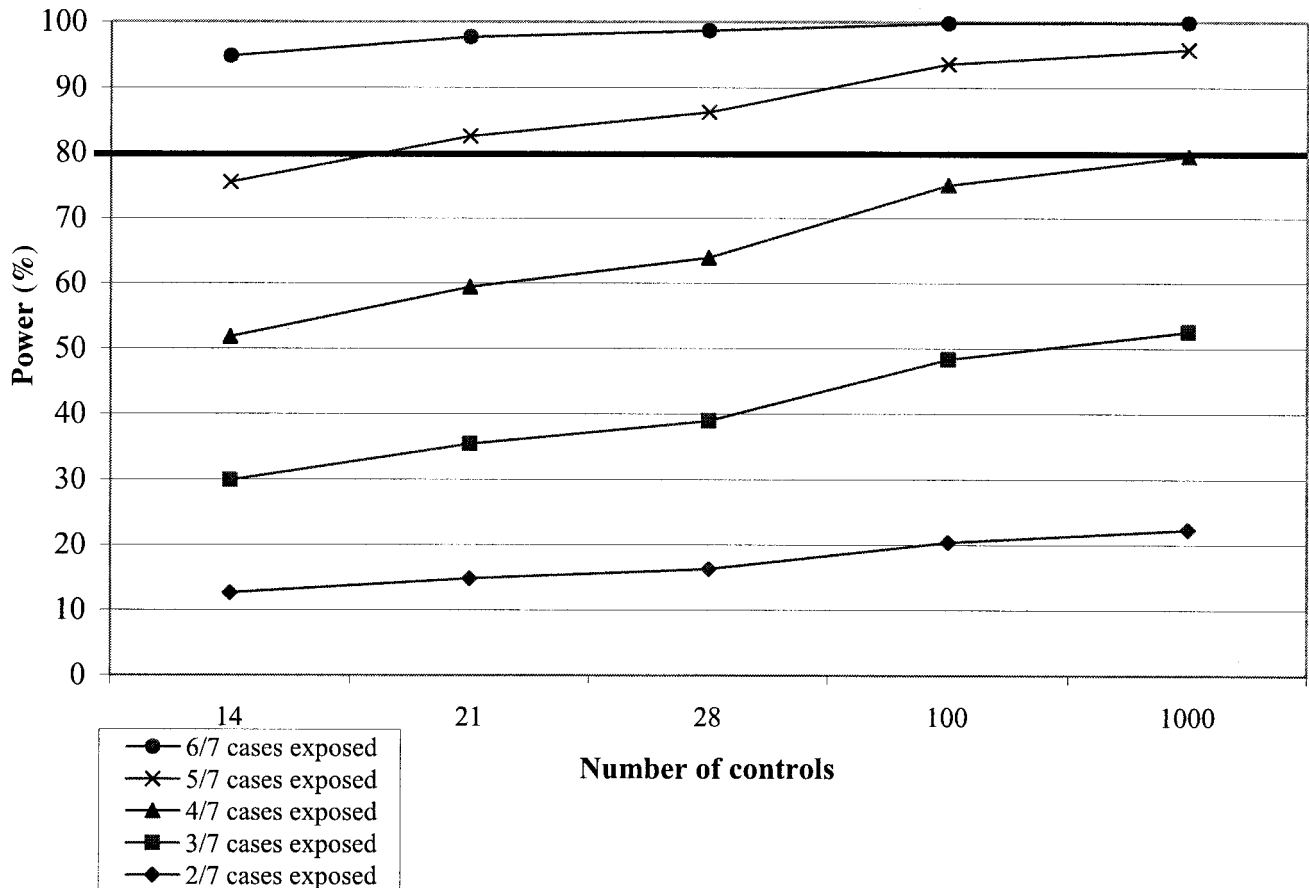


Fig. 2. Power curves for a cluster of 7 cases and 14, 21, 28, 100, and 1000 controls, assuming 15% of controls are exposed.

TABLE 2. Prevalence of selected birth defects\*

Defect	Prevalence (per 1000 births)
Down syndrome	1.25
Cleft lip with or without cleft palate	0.90
Neural tube defects	0.65
Ventricular septal defect	3.47
Urinary tract defects	2.97
Clubfoot and related foot deformities	1.62
Limb reduction defects	0.53
Gastroschisis	0.16
Craniosynostosis	0.42

\*Data from the Metropolitan Atlanta Congenital Defects Program (1995–1999), (unpublished).

and easily. However, the small number of cases in most clusters limits statistical power to detect an association, making conclusive results difficult to determine. Investigations also require more time to complete than expected. Thus, realistic expectations of how long it may take to reach a conclusion and what can and cannot be learned from a cluster investigation should be communicated to the community. Affected parents are often seeking to understand

why their child was affected with a birth defect; cluster investigations cannot answer that question. However, they may be able to determine that an excess of cases has not occurred, that a suspected environmental exposure is not to blame for an excess of cases, or in rare circumstances, that an exposure to an identifiable teratogen did occur.

When corresponding with the affected community or media, the investigator's message should be kept clear and simple. Lengthy explanations of epidemiologic methods and concepts, such as power, can lead to additional confusion. Fears and concerns can only be dispelled if the community understands the intended message. Responses should be prepared before requests for information are made, particularly when speaking with the media, in order to maintain consistency between reports.

Developing a standardized protocol for the investigation of birth defects clusters can lead to the appropriate use of resources to promote the scientific study of risk factors associated with birth defects. The recommendations made in this report should be carefully considered to ensure that the specific needs of the region, agency, and affected community are met.



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